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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,571	03/03/2004	Neil T Dear	ABB10010P0630US	9704

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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,571	DEAR ET AL.	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *dec 12 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment and Request for Continuing Examination of February 19, 2009, in response to the Final Rejection of this case mailed November 14, 2007, is acknowledged. It is acknowledged that no claims have been cancelled, amended, or added. Claims 1-6 are pending. Claim 6 was previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1-5 are hereby reconsidered.

Drawings

Objection to Figure 1 for disclosing sequences that are not identified by a sequence identifier number (SEQ ID NO:) is maintained; corrections have not been made.

Specification-Objections

Objection to the specification for improper formatting is maintained; corrections have not been made.

Objection to the specification for containing hyperlinks is maintained; corrections have not been made.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Utility

Rejection of Claims 1-5 under 35 U.S.C. 101/112 because the claimed invention lacks patentable utility, for the reasons set forth in the prior actions, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(A) The threshold for utility is low. To be patentable the invention must only have a specific, substantial, and credible utility.

(B) Applicants' assertion of utility creates a presumption of utility unless (A) the logic underlying the assertion is flawed or (B) the facts upon which the assertion is based are inconsistent with the underlying assertion (MPEP 2107.02(III)(B)). The asserted utility for the recited protein, including use for identifying inhibitors selective for CAPN11 and subsequent use of the inhibitors in treatment of disorders associated with CAPN11 activity, are credible.

(C) [Office personnel should distinguish between situations where an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful.] (See, MPEP §2107.01(I)(A)). While a general statement of diagnostic utility, without disclosure of what condition can be diagnosed is insufficient to demonstrate specific utility, a specific utility is present where the specification discloses a specific biological activity and reasonably correlates the activity to a disease condition. Any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (See, MPEP §2107.01(I)(B)).

A specific and substantial utility is provided by demonstrating that CAPN11 is most strongly expressed in testis and which chromosome the CAPN11 gene is located on in conjunction with the prior art, which shows that calpains in other tissues are involved in processes such as germ cell apoptosis and regulation of tissue-specific transcription factors. Thus, it is reasonable to suggest that CAPN11 is involved in similar processes in testis.

The polypeptides claimed in the invention have specific and substantial utility, for example as bait for identifying substances that are able to inhibit enzymatic activity of the polypeptide and, thus can be used to treat disorders due to over expression of CAPN11, such as male infertility (specification, pg 4, lines 1-26).

Applicants are not claiming that CAPN11 is useful in treating unspecified disorders, or that the protein has unspecified useful properties. In contrast, the application discloses a relation to specific processes, such as germ cell apoptosis. Cysteine proteases are known to be involved in apoptosis *(Billing et al, Human Reprod. Update, VoL 2, No. 2, pp. 103-107 (1996) and Martin et al, Cell, Vol. 82, pp. 349-352 (1995)).* The use of the invention to advance treatment of the specified disease (for example, male infertility) is providing a public benefit. The use of inhibitors of CAPN11 activity to treat infertility inherently demonstrates utility for the protein CAPN11.

Applicants' Response to the Offices' Arguments

(D) – (A) Applicants disagree with the position that RNA encoding the protein of SEQ ID NO:2 is not specific for testis. Northern blot demonstrates a very strong band in the testis lane (Fig. 3D). The significance of weaker signals in the thymus and the mammary gland is unclear because further investigation of thymus RNA produced no signal. This weak signal is probably attributable to cross-hybridization with related mRNAs (See, specification, page 2, line 45 to page 3, line 4). As the specification states, testis is the main expression site of CAPN11.

Applicants respectfully disagree that the protein of SEQ ID NO:2 cannot be used for identifying inhibitors because an assay for measuring activity has not been provided. Enzyme

activity can be determined by time dependent measurements of substrate and product concentrations. Values such as extinction, potential, and conductivity are routinely measured; photometrical methods are well known and can be applied to the claimed subject-matter.

(E) – (B) It is acknowledged that the physiological functions of all calpains is unclear (Branca et al). However, Applicants are not claiming all calpains or relying on the fact that all physiological functions of all calpains are clear. Rather, Applicants suggest that the physiological function of CAPN11 is sufficiently well-established to meet the §101 standard based on its preferential expression in testis. See Ben-Aharon (pg 772, right column) stating CAPN11 is likely "involved in regulating key signal transduction events and processes of cytoskeletal remodeling during meiosis, spermiogenesis and sperm function".

(F) – (C) See section (C) of the response filed August 30, 2007.

(G) – (D) No other evidence is required to prove patentable utility.

(H)- (E) Methods for determining substrates and assay conditions are known in the art. The skilled artisan is enabled for identifying inhibitors. The claims do not recite treatment of diseases; thus, treatment of a disease need not be enabled.

(I) – (F) The fact that Honbou et al was published after the filing date is irrelevant. The reference supports Applicants' position that CAPN11 is related to treatment of fertility by demonstrating that a related protein is related to male fertility. The fact that Honbou's protein can be used to treat several diseases does not negate its utility or the utility of CAPN11.

These arguments are not found to be persuasive for the following reasons.

(A) Reply: It is acknowledged that the threshold for utility is low. However, for an invention to have a patentable utility, it must have a specific, substantial, and credible utility. For the reasons explained below and in the prior actions the polypeptide of SEQ ID NO: 2 does not have a specific, substantial, and credible utility.

(B) Reply: It is acknowledged that there is a presumption of utility. Applicants have asserted that the polypeptide of SEQ ID NO: 2 is a calpain-family protease (Title; specification, pg 1, pargs 2 & 6). Based on the alignment of SEQ ID NO: 2 with other calpain proteins, as well as conservation of the conserved catalytic Cys-His-Asn triad, Applicants' assertion that the polypeptide of SEQ ID NO: 2 is a calpain-family protease is credible. However, as explained in the prior actions and below, assertion that the polypeptide is a calpain-family protease is not an assertion of a specific and substantial utility; therefore, the logic underlying Applicants' assertion of a patentable utility is flawed. As acknowledged by Applicants (pg 1, parg 4) and taught by the prior art (Goll et al, 2003; pg 771, parg 4), the calpain-family is large and functionally diverse; in many cases, the cellular function of calpain-family proteins is not even known. The specification fails to provide evidence of a specific and substantial utility for the protein of SEQ ID NO: 2 or any inhibitor thereof. Because the protein of SEQ ID NO: 2 fails to have a specific and substantial utility, treatment with any inhibitor thereof is not credible.

(C) Reply: The Office has, in fact, distinguished the instant situation as one where the Applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful. In the instant case, Applicants have merely asserted that the protein set forth by SEQ ID NO: 2 can be used to identify inhibitors of a testis-related disease or condition without, except for showing that the encoding polynucleotide is expressed in testis,

identifying with specificity any disease or condition to be treated. Identification of inhibitors is not a substantial use unless there is a substantial use for the inhibitors.

The skilled artisan would know that identification of chromosome localization alone cannot provide a specific and substantial utility. It is acknowledged that some calpain proteases are involved in apoptosis and regulation of gene expression. However, as explained previously, the calpain-family is a large and functionally diverse family of proteases. The fact that some calpain proteases of this large and variable family are involved in apoptosis and regulation of gene expression would not convince the skilled artisan that, more likely than not, the polypeptide of SEQ ID NO: 2 is involved in apoptosis and regulation of gene expression. In addition, regulation of gene expression is not a specific and substantial utility unless it is known which genes are regulated and how; the specification fails to provide such information.

As explained herein and in the prior actions, in order to identify substances that are able to inhibit enzymatic activity of CAPN11, an artificial or biologically relevant substrate must be used. Since the specification fails to disclose an artificial or biologically relevant substrate of CAPN11, a method to identify substances that are able to inhibit enzymatic activity of CAPN11 is not enabled. Thus, methods using a CAPN11 inhibitor to treat disorders due to over expression of CAPN11, such as male infertility, are also not enabled.

It is acknowledged that the claims do not recite a method of treatment. However, Applicants have asserted that the protein of SEQ ID NO: 2 has utility based on use of the protein to identify inhibitors that can be used for treatment without disclosing a specific disease to be treated. It is acknowledged that some cysteine proteases are involved in apoptosis. However, the genus of cysteine proteases is an extremely large and functionally diverse genus of proteases.

The fact that some cysteine proteases of this extremely large and variable family are involved in apoptosis would not convince the skilled artisan that, more likely than not, the polypeptide of SEQ ID NO: 2 is involved in apoptosis. It is acknowledged that a treatment of male fertility would provide a public benefit. However, the specification fails provide evidence that would convince the skilled artisan that, more likely than not, the protein of SEQ ID NO: 2, the encoding polynucleotide, or an inhibitor of said protein have utility in the treatment of male fertility.

Applicants should submit an Information Disclosure Statement, and the references listed therein, for any art newly cited in their responses.

(D) Reply: It is acknowledged that RNA encoding SEQ ID NO: 2 is highly expressed in testis. However, said RNA appears to also be highly expressed in mammary gland and moderlately expressed in spinal cord, placenta, and fetal thymus (Fig 3A). Therefore, one cannot conclude that said RNA is specific for testis or that the protein of SEQ ID NO: 2 has a function specific to the testis.

It is acknowledged that the skilled artisan could, using known techniques, screen panels of artificial substrates for cleavage by the protein of SEQ ID NO: 2. Furthermore, if an artificial substrate cleaved by the protein of SEQ ID NO: 2 was identified in said screen, said artificial substrate could be used for identifying an inhibitor of said protein. However, there is no guarantee that said screen would identify an artificial substrate cleaved by the protein of SEQ ID NO: 2; thus, there is no guarantee that an inhibitor of the protein of SEQ ID NO: 2 can be identified. Moreover, even if an inhibitor of the protein of SEQ ID NO: 2 was identified, there would be no specific and substantial use for said inhibitor because the function of CAPN11 is not

known. Said inhibitor could merely be used for additional experimentation into the function of CAPN11 and said additional experimentation does not provide a specific and substantial utility.

(E) Reply: For the reasons explained above and in the prior actions, preferential expression is testis does not provide a specific and substantial function for the protein of SEQ ID NO: 2. See the actions of August 8, 2006 (pg 6), and January 12, 2007 (pg 4), June 1, 2007 (pg 4) regarding the teachings of Ben-Aharon et al, 2006.

(F) Reply: This is the same argument presented in (D) above. See (D) Reply, second paragraph, above.

(G) Reply: Since neither the specification nor the prior art provide evidence as to the biological substrate of the recited protein, any specific cellular process that is mediated by said protein, any specific disease mediated by alteration in said protein, or any specific disease that can be treated with said protein, the encoding polynucleotide, or an inhibitor thereof, additional evidence is needed to support a patentable utility. Applicants are invited to file a declaration under 37 CFR 1.132 providing evidence in support of any specific and substantial utility asserted in the original disclosure. (MPEP 716)

(H) Reply: See (C, parg 3) and (D), above.

(I) Reply: For an invention to be patentable, it must have utility at the time of filing of the application (MPEP 2107(II)(B)(3)(ii)). Although a declaration under 37 CFR 1.132 providing evidence in support of any specific and substantial utility asserted in the original disclosure is proper (MPEP 716), Applicants cannot rely on post filing evidence by others. In

such a situation, Applicants are merely asserting a utility and leaving to the public the work of obtaining evidence for the asserted utility.

For these reasons and those explained in the prior action, rejection of Claims 1-5 under 35 U.S.C. 101/112 because the claimed invention lacks a substantial and specific utility is maintained.

Written Description

Rejection of Claims 4 and 5 under 35 U.S.C. 112, first paragraph/written description, as described in the prior actions, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following argument.

The specification (page 4) clearly discloses that CAPN11 is a calcium-dependent protease and that a CAPN11 selective compound is defined as a compound that selectively blocks the activity of CAPN11 at least 10-fold. Methods for detecting protease activity are known in the art. Thus, a method of identifying an inhibitor, as recited in Claims 4 and 5, is disclosed.

This argument is not found to be persuasive for the following reasons.

Mere assertion that a protein is a calcium-dependent protease does not put Applicants in possession of a method to identify inhibitors of said protease.

It is acknowledged that methods for detecting protease activity are known in the art. However, the specification fails to disclose such a method or a substrate to be used in such a method. While methods for screening panels of artificial substrates for cleavage by a protease are known, Applicants also fail to disclose such a method. In addition, such a method may not

be successful in identifying an artificial substrate cleaved by CAPN11 and no artificial or biologically-relevant substrate of CAPN11 is disclosed by the specification. Since an artificial or biologically-relevant substrate of CAPN11 is required in any method for identifying an inhibitor of CAPN11, Applicants were clearly not in possession, at the time of filing of a method for identifying an inhibitor of CAPN11.

Allowable Subject Matter

No claims are allowable.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Any new references were cited solely to reject amended claims or rebut Applicants' arguments. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652